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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P-INCI-X-04-0272	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/008509	International filing date *(day/month/year)* 29.07.2004	Priority date *(day/month/year)* 30.07.2003
International Patent Classification (IPC) or national classification and IPC A61K31/185, A61K31/44, A61K31/4184, A61P15/00, A61P15/10		
Applicant LABORATORIOS DEL DR. ESTEVE S.A. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the International application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.02.2005	30.06.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Telephone No. +49 89 2399- 7346 Paul-Soto

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/008509

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-19 as originally filed

   Claims, Numbers

   1-45 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/008509

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	13, 17-31, 34-45
	No:	Claims	1-12, 14-16, 32, 33
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-45
Industrial applicability (IA)	Yes:	Claims	1-45
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: WO 03/004097 A (ESTEVE-SOLER JOSE ; ESTEVE LABOR DR (ES); SAENZ DE TEJADA-GORMAN INIGO) 16 January 2003 (2003-01-16)

D2: ANGULO J ET AL: "Calcium dobesilate potentiates endothelium-derived hyperpolarizing factor-mediated relaxation of human penile resistance arteries" BRITISH JOURNAL OF PHARMACOLOGY, BASINGSTOKE, HANTS, GB, vol. 139, no. 4, June 2003 (2003-06), pages 854-862, XP001189343 ISSN: 0007-1188

D3: US-A-6 147 112 (ESTEVE-SOLER JOSE) 14 November 2000 (2000-11-14)

D4: CA-A-2 325 930 (KIM JE JONG ; LG CHEMICAL LTD (KR); MOON DU GEON (KR)) 29 July 2001 (2001-07-29)

D5: MOON D G ET AL: "AKATP-channel opener as a potential treatment modality for erectile dysfunction" BJU INTERNATIONAL, vol. 83, no. 7, May 1999 (1999-05), pages 837-841, XP002302506 ISSN: 1464-4096

D6: WO 02/17963 A (PFIZER LTD ; MAW GRAHAM NIGEL (GB); WAYMAN CHRISTOPHER PETER (GB); PFI) 7 March 2002 (2002-03-07)

D7: CHRIST GEORGE J: "K channels as molecular targets for the treatment of erectile dysfunction" JOURNAL OF ANDROLOGY, vol. 23, no. 5, September 2002 (2002-09), pages S10-S19, XP009038874 ISSN: 0196-3635

D8: SPEKTOR MARIYA ET AL: "Potassium channels and human corporeal smooth muscle cell tone: Further evidence of the physiological relevance of the Maxi-K channel subtype to the regulation of human corporeal smooth muscle tone in vitro" JOURNAL OF UROLOGY, vol. 167, no. 6, June 2002 (2002-06), pages 2628-2635, XP009038916 ISSN: 0022-5347

2. The present application relates to:

(I) an active substance combination comprising (A) at least one 2,5-dihydroxybenzenesulfonic compound of the given general formula I, and (B) at least one potassium ion (K+) channel modulator (**claim 1**);

(ii) a medicament comprising said active substance combination and optionally at least one further active substance and /or at least one auxiliary (**claim 10**); and for the prophylaxis and/or treatment of male sexual dysfunction, female sexual

dysfunction and the rest of diseases referred to in **claim 11**;

(iii) **claims 12-31** are drafted in the second-medical use format for the same diseases;

(iv) pharmaceutical formulation comprising said active substance combination and optionally at least one further active substance and/or optionally at least one auxiliary (**claim 33**).

3.1. The present application does not meet the requirements of the PCT with respect to novelty (Art. 33(2)) for the following reasons.

D1 discloses the use of 2,5-dihydroxybenzenesulphonic derivates such as calcium dobesilate, ethamsylate and persilate to potentiate the effect of other drugs in the treatment of erectile dysfunction. Nicorandil (which is a potassium channel opener) is one of the drugs specifically disclosed. Thus, **D1** is novelty destroying for present claims 1-12 and 32.

D2 discloses the use of calcium dobesilate for oral therapy, for erectile dysfunction. The document discloses experiments in which calcium dobesilate is administered in combination with agents that modulate potassium channels. This is regarded as novelty destroying for present claims 1-3, 8, 10-12, 14-16, 32 and 33.

3.2. Present claims 13, 17-31 and 34-45 appear to be novel over the prior art.

4. The present application does also not meet the requirements of the PCT with respect to inventive step (Art. 33(3)) for the following reasons.

2,5-dihydroxybenzenesulphonic derivates and specifically calcium dobesilate, ethamsylate and persilate are well known in the art as active agents for the treatment of male sexual dysfunction and other vascular disorders of endothelial origin, both alone and in combination with other agents (see for example **D1**, **D2**, and **D3**). The present application according to **claim 1** differs from the prior art in that the 2,5-dihydroxybenzenesulphonic derivates are combined with at least one potassium ion channel modulator.

Thus, the *problem* to be solved by the present application can be regarded in the provision of alternative pharmaceutical compositions for the treatment of male sexual dysfunction. The solution provided by the present application according to

claim 1 is rendered obvious by the prior art. Several documents of the prior art (see for example **D4**, **D5** and **D6**) disclose that potassium channel openers are useful for the treatment of male sexual dysfunction. Thus, the combination proposed in the present application would be obvious to the skilled person since the two agents are known for the same therapeutic indication. The specific selection of pinacidil or NS1619 as potassium channel openers does also not appear to involve an inventive step in the light of **D7** and **D8**. The rest of technical features in the dependent claims merely consist in the selection of particularly preferred embodiments which are determined empirically, without the exercise of inventive skill, or fall anyway within the customary practise followed by those skilled in the art.

The applicant should note that in the present case an inventive step can only be recognised if an advantage or surprising effect arises from the combination. The application mentions a synergistic effect (see page 19) in connection with the treatment of erectile dysfunction. However, this effect is not substantiated by any technical evidence and, as such, cannot be taken into account for the assessment of inventive step. Similarly, no such effect is disclosed in connection with the rest of therapeutic indications referred to in present claims 13-31 (no technical data disclosed at all).

5.1. For the assessment of the present **claims 12-31** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5.2. Claims 1-11 and 32-45 meet the criterion set forth in Article 33(4) PCT because their subject-matter is susceptible of industrial application.

Re Item VIII

Certain observations on the international application

6. Present claim 7 does not meet the requirements of Art. 6 PCT because its

subject-matter is not clearly defined. Said claim refers to benzimidazole derivatives of a general formula I and then, to a list of preferred compounds, most of which do not fall within the general formula I specified before.